Sub C1

109. (New) The composition of Claim 108, wherein at least one of said oligonucleotides comprises a 5' phosphate.

REMARKS

The specification has been amended to correct minor obvious errors. No new matter has been added.

Claims 12, 18, 21, 22, 24, 27, 28, 30, 31, 33-50, 53-56, 59-62, 65-68, 70, 73, 74, 80, 84, 87 and 90-92 have been canceled. Claims 1, 2, 4, 6-8, 13, 14, 19, 20, 23, 25, 26, 29, 32, 51, 57, 63, 69, 71, 75, 76, 83, 85, 86 and 88 have been amended. Claims 93-109 have been added.

Claims 7 and 14 have been amended to indicate, more particularly, that the epidermal cells producing melanin are melanocytes. See page 1, lines 15-19 of the specification.

Claim 93 is supported by Figure 18, and page 34, line 15 to page 35, line 5.

Claims 94 and 98 are supported by page 27, line 11 to page 28, line 27; page 39, line 24 to page 40, line 12; and page 40, line 25 to page 41, line 10.

Claims 95, 96 and 97 are supported by Examples 1-3 (page 20, line 10 to page 22, line 25), Figures 1-4, page 36, line 19 to page 37, line 3 and Figures 13 and 14.

Claim 99 finds support in Examples 1, 2 and 3, (page 20, line 10 to page 22, line 25, and Figures 1-4) Example 4 (page 23, lines 2-8), Example 5 (page 23, line 16 to page 24, line 6) and Example 12 (page 36, line 21 to page 37, line 3).

Support for Claim 100 can be found in Examples 1, 2 and 3, (page 20, line 10 to page 22, line 25, and Figures 1-4) Example 4 (page 23, lines 2-8), Example 5 (page 23, line 16 to page 24, line 6), Example 6 (page 24, line 8 to page 25, line numbered as "5") and Example 12 (page 36, line 21 to page 37, line 3).

Support for Claim 101 is found at page 36, line 19 to page 37, line 3, for instance.

Support for Claim 102 can be found in Examples 3, 4, 5 and 6 (page 22, line 18 to page 25, line numbered as "5").

Claim 103 is supported by Examples 3, 4 and 5 (page 22, line 18 to page 24, line 6).

Claims 104 and 105 are supported by Example 12 (page 36, line 21 to page 37, line 3).

Claims 106, 107, 108 and 109 find support on page 36, lines 1-4, for example.

Supplemental Information Disclosure Statement

The Examiner has pointed out an error in the citation of journal article AY2 in the Information Disclosure Statement mailed to the United States Patent and Trademark Office on December 12, 2000. A Second Supplemental Information Disclosure Statement giving the correct citation for this journal article was mailed to the U.S. Patent and Trademark Office on August 20, 2002. Entry of the Second Supplemental Information Disclosure Statement is respectfully requested. The Examiner is asked to disregard the previously cited reference AY2.

Specification

The Examiner has pointed out typographical errors in the specification. The specification has been amended to correct typographical errors.

Claim Objections

Claims 1, 2, 57, 58 and 69 have been objected to because of informalities.

Claim 1 is said to read on non-elected species. Claim 1 has been amended.

Claims 2, 57, 58 and 69 are said to recite SEQ ID NO:3 and SEQ ID NO:7, which are the same sequence. Claims 2 and 57 have been amended to recite SEQ ID NO:3 but not SEQ ID NO:7.

Rejection of Claims 1-4, 6, 14-16, 19, 57-58, 69, 75, 83 and 88 on the Basis of Obviousness-Type Double Patenting

Claims 1-4, 6, 14-16, 19, 57-58, 69, 75, 83 and 88 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over either Claims 2, 3 or 5 of U.S. Patent No. 6,147,056.

A Terminal Disclaimer is being filed with this Amendment, in which the owner of the instant application disclaims the terminal part of the statuory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of U.S. Patent No. 6,147,056.

Rejection of Claims 1, 3-4, 6 and 85-86 on the Basis of Obviousness-Type Double Patenting

Claims 1, 3-4, 6 and 85-86 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 11-14 and 20-25 of US Patent No. 5,955,059.

A Terminal Disclaimer is being filed with this Amendment, in which the owner of the instant application disclaims the terminal part of the statuory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of U.S. Patent No. 5,955,059.

Rejection of Claims 1, 5, 14 and 17 Under Obviousness-Type Double Patenting

Claims 1, 5, 14 and 17 have been rejected "under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2 and 3 of U.S. Patent No. 6,147,056 in view of Iversen *et al.* (US Patent No. 5,643,890, IDS)."

A Terminal Disclaimer is being filed with this Amendment, in which the owner of the instant application disclaims the terminal part of the statuory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of U.S. Patent No. 6,147,056.

Rejection of Claims 75 and 77-78 Under Obviousness-Type Double Patenting

Claims 75 and 77-78 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 5 of U.S. Patent No. 6,147,056 in view of "applicants' own admission that liposomes such as those described in US Patent No. 5,077,211 of Yarosh can be used (page 14, lines 13-17)."

A Terminal Disclaimer is being filed with this Amendment, in which the owner of the instant application disclaims the terminal part of the statuory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of U.S. Patent No. 6,147,056.

Rejection of Claims 75 and 77-79 Under Obviousness-Type Double Patenting

Claims 75 and 77-79 have been rejected under the judicially created doctrine of obviousness-type double patenting "as being unpatentable over claim 5 of U.S. Patent No. 6,147,056 in view of West et al. (US Patent No. 6,194,206)."

A Terminal Disclaimer is being filed with this Amendment, in which the owner of the instant application disclaims the terminal part of the statuory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of U.S. Patent No. 6,147,056.

Rejection of Claims 85 and 89 Under Obviousness-Type Double Patenting

Claims 85 and 89 have been rejected under the judicially created doctrine of obviousness-type double patenting "as being unpatentable over claim 5 of U.S. Patent No. 6,147,056 in view of Beer-Romero *et al.* (US Patent No. 5,858,987)."

A Terminal Disclaimer is being filed with this Amendment, in which the owner of the instant application disclaims the terminal part of the statuory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of U.S. Patent No. 6,147,056.

Rejection of Claims 1-11, 13-17, 19-23, 25-29, 31-32, 51-52, 57-58, 63-64, 69, 71-83, 85-86 and 88-89 Under 35 U.S.C. § 112, First Paragraph

Claims 1-11, 13-17, 19-23, 25-29, 31-32, 51-52, 57-58, 63-64, 69, 71-83 and 85-86 and 88-89 have been rejected under 35 U.S.C. § 112, first paragraph, as it is said that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Examiner states that for Claims 7, 9-11 and 13, the specification is not sufficient to support the present claimed invention as directed to a genus of a mimic of telomere disruption. Independent Claim 7 has been amended to more particularly define the invention. Claim 13 has been amended. Claim 12 has been canceled. As amended Claim 7 is drawn to a method of increasing melanin production in epidermal cells that employs SEQ ID NO:5, SEQ ID NO:3, or SEQ ID NO:11.

Claim 93 is similar to Claim 7. The meaning of "nucleotide sequence homologous to the telomere repeat sequence" in Claim 93 is understood by one of ordinary skill in the art. The telomere repeat sequence is known. Applicants have provided several examples of several melanogenic oligonucleotides having a nucleotide sequence homologous to the telomere repeat sequence. For example, the oligonucleotides having the following sequences were found to be melanogenic: pTpT, SEQ ID NO:1, SEQ ID NO:5 and SEQ ID NO:11 (Example 12; page 35, line 10 to page 36, line 4).

The Examiner states that in the art of administering oligonucleotides, relatively little is known about the in vivo behavior of the oligonucleotide (first paragraph, page 17 of Office Action). The Examiner raises concerns about degradation and side interactions with proteins and mRNAs that are not the "target."

In Example 14, page 39, line 24 to page 40, line 12, Applicants demonstrated that oligonucleotides can be administered to guinea pigs with a measurable biological effect on the skin. Also see the experiments on mice described on page 36, lines 5-17. From these demonstrations, it can be concluded that adjustments of dosages and regimens of administration of the oligonucleotides should be straightforward.

The Examiner states (second paragraph, page 17 of Office Action) that there have been some conflicting results found in the prior art, using the oligomer with sequence TTAGGG (SEQ ID NO:11) to inhibit cell proliferation. The Examiner points out that oligonucleotides having a nucleotide sequence resembling that of the telomere repeat have been tested previously for inhibiting cell proliferation, with varying results depending on cell type (paragraph bridging pages 17-18 of Office Action). However, none of the claims in question include a recitation that the oligonucleotide must inhibit telomerase or interact with any specific target molecule.

The Examiner includes a discussion of problems with gene therapy (page 18, line 10 to page 19, line 10 of Office Action). The methods of the claims do not require the use of oligonucleotides known to be part of a coding region or a non-coding region of a gene. Applicants do not recite in the claims or discuss anywhere in the specification a mechanism in which the oligonucleotides must integrate into the existing DNA of the target cells, or interact with a specific target molecule of the target cells. The mechanism by which the oligonucleotides

exert the effects in the claimed methods is not recited in the claims, but is, in all likelihood, something that cannot be called "gene therapy."

The Examiner states (page 20, last paragraph, concluding on page 21 of Office Action) that oligonucleotides with one of several recited sequences (SEQ ID NOs. 1, 3, 6 and 11) were seen to stimulate melanogenesis. Claim 7 has been amended to recite oligonucleotides of specific sequences among those recited by the Examiner.

With respect to Claim 86, the Examiner outlines expected difficulties in a method of preventing or reducing DNA damage caused by UV-irradiation in cells other than skin cells. Claim 86 has been amended to make clear that the DNA damage is to epidermal cells of a mammal.

The Examiner points out some concerns that would perhaps be relevant to methods employing oligonucleotides in antisense nucleic acid therapy. For example, the Examiner states that the specification (see page 23, lines 6-9) "does not provide sufficient guidance for one skilled in the art to ... target a particular pathway in that cell that could use the therapeutic amount of either T2 or SEQ ID NO:1 . . . ." This is not a requirement for enablement.

The Examiner also cites a US patent (5,585,479) that (see page 24, lines 2-4 of Office Action) "provide[s] reasons to support the lack of reasonable correlation between the primary structure of an oligonucleotide and its activity in vivo." The cited patent describes antisense oligonucleotides intended to bind to a known mRNA. The Examiner also cites the review article by Branch and concludes from its discussion on design of antisense molecules intended to bind to target mRNAs that "determination of DNA sequences effective for use in any therapeutic method remains unpredictable." Applicants have not postulated a mechanism of action or target for the oligonucleotides used in the claimed methods. It cannot be assumed that the difficulties found in antisense oligonucleotide methods will apply to the methods of the claims.

With regard to Claims 71-74, the Examiner states on page 27, "In view of the guidance provided by the disclosures and the breadth of the claims, it would require an undue amount of experimentation for one skilled in the art to reasonably extrapolate that a therapeutic effect would be observed in vivo in any cell other than epithelial cells because of the concerns stated by the art of record." The Examiner further states, ". . . it would take one skilled in the art an undue amount of experimentation to reasonably correlate to any fragment of about 2 to about 200

nucleotides other than the three distinct fragments set forth in the working examples." Claim 71 has been amended to better define the invention. Claims 73 and 74 have been canceled.

The Examiner states, with respect to Claims 20-25,

> Therefore, in view of the art of record, the as-filed specification is only enabled for a method of increasing DNA repair in skin cells by topically or directly administering T2 to said skin cells and the claimed invention is not enabled for using any other DNA fragment (SEQ ID NO:5 or 7) in a method for increasing DNA repair in skin cells because the specification only provides sufficient guidance for one skilled in the art to use several distinct oligonucleotide sequences for increasing melanin production and therefore, it would take one skilled in the art an undue amount of experimentation to reasonably correlate the results observed with T2 to SEQ ID NOs 5 and 7 because of the art of record set forth above.

As the Examiner points out, Example 8 of the specification reports the use of "a UV-damaged reporter plasmid to measure the DNA repair capacity of normal cells. The data from the assays displayed that T2 treatment of cells in vitro can double the capacity of cells to repair UV-induced DNA damage over a 24 hour period." Claims 21, 22 and 24 have been canceled.

The oligonucleotide of sequence SEQ ID NO:1 also was effective in increasing DNA repair in skin cells. See Example 16 on page 40, line 25 to page 41, line 10. Claim 94 has been added.

The Examiner states, regarding Claim 88,

> ". . . the as-filed specification is only enabled for treating skin cells by topically administering to said skin cells or directly administering DNA fragments selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotide dimers and combinations thereof to epithelial cells because other routes of administration such as orally, intravenously, instillation into the bladder, etc. would expose the fragments to the acidity of the stomach, the host's immune response, the blood stream, which would result in the degradation of the fragments and the fragments would not reach the target cell at a therapeutic level. Therefore, the claimed invention is only enabled for a method of inhibiting malignant cells of a mammal, comprising topically administering to skin cells or directly administering to the epithelial cells of the mammal an effective amount of DNA fragments that are approximately 2-200 bases in length, the DNA fragments being selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides and dinucleotide dimers and combinations thereof."

Claim 88 has been amended to clarify the invention. Claims 95, 96 and 97 have been added. The administration of oligonucleotides to target sites of a mammal has not been the major obstacle envisioned by the Examiner. See the review article enclosed as Exhibit A, Hogrefe, R.I., *Antisense and Nucleic Acid Drug Development 9*:351-357, 1999. See especially page 352, column 1, line 3 to page 353, column 1, line 12 and Table 1 on page 352 presenting evidence that routes of administration of synthetic oligonucleotides have been successful. The Hogrefe review shows that, in clinical trials, several types of malignancies have been treated by oligonucleotides administered by known routes of administration other than topical administration, and that these in vivo routes of administration have been effective.

With regard to Claims 26-29 and 31-32, the Examiner states that "the disclosure does not teach one skilled in the art how to use DNA fragments in any route of administration other than topically or directly." As pointed out above, several routes of administration have been used to deliver oligonucleotides to a number of different organs. One of ordinary skill in the art could turn to reports on such studies for guidance in delivery of effective amounts of oligonucleotides to epithelial cells at sites other than the skin.

The Examiner states that Claims 85 and 89 "are only enabled for a method of inhibiting proliferation of epidermis epithelial cells comprising topically administering or directly administering to said cells an effective amount of DNA fragments selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, and dinucleotide dimers and combinations thereof." Claim 85 has been amended to better define the invention.

The Examiner states that Claim 76 is not enabled by the as-filed specification because the recited oligonucleotides do not have two adjacent pyrimidine residues to allow photodimerization from ultraviolet irradiation. Claim 76 has been amended to recite an oligonucleotide with two adjacent pyrimidine residues.

Rejection of Claims 4 and 13 Under 35 U.S.C. § 112, Second Paragraph

Claims 4 and 13 have been rejected under 35 U.S.C. § 112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is said to be indefinite for reciting "the polynucleotide" without sufficient antecedent basis. The term "polynucleotide" has been changed to "oligonucleotide," for which there is antecedent basis.

Claim 13 is said to be indefinite for reciting "the inhibitor" without sufficient antecedent basis. Claim 13 has been amended, and as amended, does not recite this term.

Rejection of Claims 51-52 Under 35 U.S.C. § 102(a)

Claims 51-52 have been rejected under 35 U.S.C. § 102(a) "as being anticipated by Shay *et al.* (U.S. Patent No. 6,015,710)."

Shay *et al.* teach an 11-mer peptide nucleic acid with base sequence GTTAGGGTTAG. Shay *et al.* do not discuss other types of oligonucleotide analogs or phosphodiester backbone oligonucleotides.

Claim 51 has been amended to make clear that the oligonucleotide in the claimed composition has a phosphodiester backbone. Therefore, Claim 51 and dependent Claim 52 are not anticipated by Shay *et al.* (U.S. Patent No. 6,015,710).

Rejection of Claims 51-52 Under 35 U.S.C. § 102(e)

Claims 51-52 have been rejected under 35 U.S.C. § 102(e) "as being anticipated by Shay *et al.* (U.S. Patent No. 6,046,307)."

Shay *et al.* teach the 11-mer peptide nucleic acid with base sequence GTTAGGGTTAG. Shay *et al.* do not discuss other types of oligonucleotide analogs or phosphodiester backbone oligonucleotides.

Claim 51 has been amended to make clear that the oligonucleotide in the claimed composition has a phosphodiester backbone. Therefore, Claim 51 and dependent Claim 52 are not anticipated by Shay *et al.* (U.S. Patent No. 6,046,307).

Rejection of Claim 85 Under 35 U.S.C. § 102(e)

Claim 85 has been rejected under 35 U.S.C. § 102(e) "as being anticipated by Beer-Romero *et al.* (U.S. Patent No. 5,858,987)."

Beer-Romero *et al.* teach administering to cells an E6AP antisense construct, of which at least a portion is complementary to an E6AP gene. Inhibition of the E6AP gene would result in the regulation of cell proliferation and/or cell viability, of cells expressing p53.

Claim 85 has been amended, and as amended, does not encompass the method of Beer-Romero, as their method only employed single-stranded oligonucleotides.

Rejection of Claim 88 Under 35 U.S.C. § 102(e)

Claim 88 has been rejected under 35 U.S.C. § 102(e) "as being anticipated by Iversen *et al.* (U.S. Patent No. 5,643,890)." Claim 88 has been amended to better define the invention. As amended, Claim 88 is drawn to treating malignant cells of a mammal, using DNA fragments with phosphodiester backbones.

The oligonucleotides of Iversen *et al.* are phosphorothioate oligonucleotides. See column 4, lines 25-35. The Iversen *et al.* patent describes a method to inhibit proliferation of cells using oligonucleotides with phosphorothioate backbones, wherein the oligonucleotides have base sequences resembling the telomere repeat sequence. The patent also describes experiments in which oligonucleotides having phosphodiester backbones were tested for their ability to inhibit proliferation of cells. The results of these experiments are shown in Figure 2. Also see Example 1, column 10. The results in Figure 2 indicate that the oligonucleotide with a phosphorothioate backbone was effective in inhibiting the growth of the OMA-BL1 cells, but not the oligonucleotide with a phosphodiester backbone. Therefore, the Iversen *et al.* patent does not disclose the method of Claim 88.

CONCLUSION

The Examiner is respectfully requested to consider the above amendments and remarks, and to withdraw the rejections. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Carol A. Egner

Carol A. Egner
Registration No. 38,866
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: September 6, 2002

MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 6, lines 14 through 15 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Figure 19 shows FACS analysis of [propiumiodide] propidium iodide stained cells, treated with 40 μM of the indicated oligonucleotide.

Replace the paragraph at page 10, lines 14 through 22 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Example 10 also demonstrates that pTpT induces production of IL-10 mRNA and protein which is active in inhibiting T cell proliferation in allogenic mixed lymphocyte assay. In human skin, IL-10 as well as TNFα induce specific tolerance for contact hypersensitivity and delayed-type hypersensitivity reactions. Therefore, the DNA fragments, oligonucleotides, deoxynucleotides, dinucleotides and [dinucletide] dinucleotide dimers of the present invention are reasonably expected to have immunosuppressive effects *in vivo*, e.g., to inhibit contact hypersensitivity and delayed-type hypersensitivity. These findings expand the spectrum of UVB effects mimicked by the compounds of the present invention.

Replace the paragraph at page 25, line 7 to page 26, line 3 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Both the GADD 45 and SDI 1 genes are known to be transcriptionally regulated by the tumor suppressor protein p53. After UV- and γ-irradiation, as well as treatment of cells with DNA-damaging chemical agents, there is a rapid stabilization and nuclear accumulation of p53 after which this protein binds to specific promoter consensus sequences and modulates the transcription of regulated genes. Recent data suggest that p53 can also be activated by the binding of small single-stranded DNAs, as well as certain peptides and antibodies, to a carboxyl terminal domain of this protein. In order to determine whether the inhibitory effect of the dinucleotide pTpT on cell proliferation is mediated through p53, the growth response of a p53 null cell line, H1299 lung carcinoma cells, was examined. The p53-null H1299 cells (Sanchez, Y. *et al., Science 271*:357-360 (1996)) [was] <u>were</u> maintained in DMEM with 10% calf serum. Preconfluent cultures were given fresh medium supplemented with either 100 μM pTpT or diluent. Cells were collected on consecutive days by trypsinization, and counted by Coulter™ counter. As shown in Figure 9, there was no inhibition of proliferation of pTpT-treated H1299 cells compared to diluent-treated controls.

Replace the paragraph at page 27, line 18 through page 28, line 13 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Newborn keratinocytes were established as described (Stanulis-Praeger, B.M. and Gilchrest, B.A., *J. Cell. Physiol. 139*:116-124 (1989)) using a modification of the method of Rheinwald and Green (Gilchrest, B.A. *et al., J. Invest. Dermatol. 101*:666-672 (1993)). First-passage keratinocytes were maintained in a non-differentiating low Ca^{2+} medium (K-Stim, Collaborative Biomedical Products, Bedford, MA). Fibroblasts were established from dermal explants as described (Rheinwald, J.G. and Green, J., *Cell 6*:331-343 (1975)) and maintained in DMEM supplemented with 10% bovine serum. Cells were treated with either 100 μM pTpT or an equal volume of diluent (DMEM) for five days prior to transfection. Duplicate cultures of each condition were transfected using the Lipofectin Reagent Kit (GIBCO/BRL) and 5 μg reporter DNA, pCAT-control vector (Promega, Madison, WI). Before transfection, the vector DNA was either sham irradiated or exposed to 100 mJ/cm^2 UVB radiation from a 1 KW Xenon arc solar simulator (XMN 1000-21,

Optical Radiation, Azuza, CA) metered at 285 ± 5 nm using a research radiometer (model IL 1700A, International Light, Newburyport, MA), as described (Yaar, M. *et al., J. Invest. Dermatol. 85*:70-74 (1985)). Cells were collected 24 hours after transfection in a lysis buffer provided in the CAT Enzyme Assay System (Promega, Madison, WI) using a protocol provided by the manufacturer. CAT enzyme activity was determined using the liquid scintillation counting protocol and components of the assay system kit. Labeled chloramphenicol [[50-60 mC1 (1.85-2.22 GBq) mmol]] [50-60 mCi (1.85-2.22 GBq)/mmol] was purchased from New England Nuclear (Boston, MA). Protein concentration in the cell extracts was determined by the method of Bradford (Anal. Biochem. 72:248 (1986)). CAT activity was expressed as c.p.m./100 μg protein and is represented as percent activity of cells transfected with sham-irradiated, non-damaged, plasmid.

Replace the paragraph at page 35, line 20 through page 36, line 4 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

pTpT, shown previously to stimulate pigmentation in these cells, was used as a reference treatment and diluent alone as a negative control. After five days of treatment with the oligonucleotides, the cells were collected, counted, and an equal number of cells were pelleted for melanin analysis. The data shown in Figure 17 demonstrate that 10 μM pTpT increased melanin content to 3 times that of control diluent-treated cells. SEQ ID NO: 5, representing the telomere over-hang sequence, also at 10 μM, increased the melanin level to 10 times that of control cells. SEQ ID NO: 9 (telomere over-hang complement) and SEQ ID NO: 10 (unrelated sequence) did not produce significant change in pigment content at concentration up to 10 μM. A truncated version of SEQ ID NO: 5, comprising TTAGGG (SEQ ID NO: 11) was also highly melanogenic, while the reverse complimentary sequence CCCTAA [(SEQ ID NO: 12,)] (SEQ ID NO:12) was less active (Figure 18), where both oligonucleotides contained a 5' phosphate).

Replace the paragraph at page 36, lines 11 through 17 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

In another experiment, mice were treated once daily with [either100μM] either 100 μM pTpT or SEQ ID NO: 1 containing a 5' phosphate in propylene glycol on one ear, or vehicle alone on the other ear. After 15 days, when the ears were sectioned and stained with Fontana Masson to detect melanin compared to vehicle controls, there was a 70% increase in pigmentation in pTpT-treated ears and a 250% increase with SEQ ID NO: 1. Thus, both compounds comprising as few as 2 and as many as 9 nucleotides are effective at producing the *in vitro* UV-mimetic effects *in vivo*.

Replace the paragraph at page 38, line 2 through page 39, line 3 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Fluorescein phosphoramidite (FAM) labeled oligonucleotides were added to cultures of S91 cells for 4 hours and the cells were then prepared for confocal microscopy. Nuclei, identified by staining with propidium iodide, appeared red and FAM-labeled oligonucleotides appeared green. Co-localization of red and green signals was assigned a yellow color by the computer. Oligonucleotides with a 5' phosphate showed greater cellular uptake than those lacking this moiety. Confocal microscopy failed to detect uptake of TpT and fluorescence-activated cell sorting (FACS) analysis of these cells and gave a profile similar to that seen with untreated cells. pTpT-treated cells showed strong green fluorescence in the cytoplasm, but only a small amount of nuclear localization. FACS analysis showed a shift in the peak fluorescence intensity, compared to TpT-treated cells, indicating more intensely stained cells. Similarly, the presence of the phosphate at the 5' end of SEQ ID NO: 1 greatly enhanced its uptake into the S91 cells. SEQ ID NO: 1 without 5' phosphorylation showed only moderate uptake and was localized predominantly in the cytoplasm, with faint nuclear staining in only some cells, whereas SEQ ID NO: 1 with 5' phosphorylation showed intense staining that strongly localized to the nucleus. FACS analysis of SEQ ID NO: 1 without 5' phosphorylation

showed a broad range of staining intensities with essentially two populations of cells, consistent with the confocal images. The phosphorylated SEQ ID NO: 1 containing cells also showed a range of staining intensities, but with more cells showing higher fluorescent intensity. Cells treated with phosphorylated SEQ ID NO: 8 showed a pattern of fluorescence very similar to that seen with phosphorylated SEQ ID NO: 1, both by confocal microscopy and FACS analysis, indicating that its lower activity in the melanogenesis assay cannot be ascribed to poor uptake. These [date] data show that uptake of these oligonucleotides by S91 cells is greatly facilitated by the presence of 5' phosphate and that melanogenic activity, while consistent with a nuclear site of action, is not solely dependent on nuclear localization. Also, although the total intracellular fluorescence did not increase appreciably with increasing oligonucleotide length among the DNAs tested, the larger oligonucleotides more readily accumulated in the cell nucleus. There was no change in the profile of oligonucleotide uptake after 6 and 24 hours.

Replace the paragraph at page 39, lines 5 through 23 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Oligonucleotides homologous to the telomere overhang repeat sequence (TAAGGG) sequence (11mer-1: SEQ ID NO: 5), complementary to this sequence (11mer-2: SEQ ID NO: 9) and unrelated to the telomere sequence (11mer-3: SEQ ID NO: 10) were tested. The three 11-mer oligonucleotides were added to cultures of Jurkat cells, a line of human T cells, one of the cell types reported to undergo apoptosis in response to telomere disruption. Within 48 hours, 50% of the cells treated with 40 μM of SEQ ID NO:5 had accumulated in the S phase, compared to 25-30% for control cells ($p<0.0003$, non-paired t-test), and by 72 hours, 13% of these cells were apoptotic as determined by a sub-G_0/G_1 DNA content, compared to 2-3% of controls ($p<0.007$, non-paired t-test) (Fig. 19). At 96 hours, 20±3% of the 11mer-1 treated cells were apoptotic compared with 3-5% of controls ($p<0.0001$, non-paired t-test). To exclude preferential uptake of the 11mer-1 as an explanation of its singular effects, Jurkat cells were treated with oligonucleotides labelled on the 3' end with fluorescein phosphoramidite, then subjected to confocal microscopy and FACS analysis.

The [fluorescent] fluorescence intensity of the cells was the same after all treatments at 4 hours and 24 hours. Western analysis showed an increase in p53 by 24 hours after addition of 11mer-1, but not 11mer-2 or -3, with a concomitant increase in the level of the E2F1 transcription factor, known to cooperate with p53 in induction of apoptosis and to induce a senescent phenotype in human fibroblasts in a p53-dependent manner as well as to regulate an S phase checkpoint.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) A method of reducing photoaging in a mammal, comprising administering to the epidermis of the mammal a composition comprising an effective amount of at least one oligonucleotide, wherein said oligonucleotide is approximately 2-200 [bases] nucleotides in length, and wherein the oligonucleotide comprises a phosphodiester backbone [selected from the group consisting of phosphorothioate, phosphorodithioate, phosphoamidate, methylphosphate and combinations thereof].

2. (Amended) The method of Claim 1, wherein said oligonucleotide comprises a nucleotide sequence consisting of a nucleotide sequence or a portion of a sequence selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 5, 6, [7,] 8, 9, 10, 11 and 12 [or portion thereof].

4. (Amended) The method of Claim 1, wherein the [polynucleotide] oligonucleotide comprises a 5' phosphate.

6. (Amended) The method of Claim 1, wherein the oligonucleotide [is provided together with] comprises a physiologically acceptable carrier.

7. (Amended) A method of increasing melanin production in epidermal [cells,] melanocytes, said method comprising topically administering to said cells an effective amount of a composition comprising at least one oligonucleotide, wherein the oligonucleotide has a phosphodiester backbone, and wherein the oligonucleotide has a nucleotide sequence

consisting of SEQ ID NO:5, SEQ ID NO:3, or SEQ ID NO:11 [comprising contacting said cells with a mimic of telomere disruption, wherein said mimic comprises at least one oligonucleotide].

8. (Amended) The method of Claim 7, wherein said oligonucleotide has a nucleotide sequence consisting of [comprises] SEQ ID NO: 5, or a portion thereof.

13. (Amended) The method of Claim 7, wherein the [inhibitor is provided together with] composition comprises a physiologically acceptable carrier.

14. (Amended) A method of increasing melanin production in epidermal [cells] melanocytes, comprising contacting the cells with an effective amount of at least one oligonucleotide having a phosphodiester backbone, wherein the oligonucleotide [comprises] consists of at least one sequence or portion thereof selected from the group consisting of: [SEQ ID NOs: 5, 7 and 8 or portion thereof] pTpT, SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:11 and SEQ ID NO:12.

19. (Amended) The method of Claim 14, wherein the [oligonucleotide is provided together with] composition comprises a physiologically acceptable carrier.

20. (Amended) A method of increasing DNA repair in epithelial cells, comprising [contacting] applying directly to said cells [with] an effective amount of a composition comprising pTpT [at least one oligonucleotide, wherein said oligonucleotide comprises a sequence selected form the group consisting of SEQ ID NOs: 5, 7 and 8].

23. (Amended) The method of Claim 20, wherein the [oligonucleotide] pTpT is at a concentration of about 1 μM to about 500 μM.

25. (Amended) The method of Claim 20, wherein the [oligonucleotide is provided together with] composition comprises a physiologically acceptable carrier.

26. (Amended) A method of inhibiting proliferation of epithelial cells, comprising [contacting] administering to said cells [with] an effective amount of a composition comprising pTpT [at least one oligonucleotide, wherein said oligonucleotide comprises a sequence selected from the group consisting of SEQ ID NO: 5, 7 and 8].

29. (Amended) The method of Claim 26, wherein the [oligonucleotide] pTpT is at a concentration of about 1 μM to about 500 μM.

32. (Amended) The method of Claim 26, wherein the [oligonucleotide is provided together with] composition comprises a physiologically acceptable carrier.

51. (Amended) A composition comprising at least one oligonucleotide, said oligonucleotide having a phosphodiester backbone, and a physiologically acceptable carrier, wherein at least one of said oligonucleotides [is] has an oligonucleotide sequence consisting of SEQ ID NO: 5 and wherein said composition is suitable for medicinal or cosmetic use.

57. (Amended) A composition comprising at least one oligonucleotide, said oligonucleotide comprising a phosphodiester backbone, and a physiologically acceptable carrier, wherein at least one of said oligonucleotides [is SEQ ID NO: 7] has a nucleotide sequence consisting of SEQ ID NO:3 and wherein said composition is suitable for medicinal or cosmetic use.

63. (Amended) A composition comprising at least one oligonucleotide, said oligonucleotide comprising a phosphodiester backbone, and a physiologically acceptable carrier, wherein at least one of said oligonucleotides [is] has a nucleotide sequence consisting of SEQ ID NO: 9 and wherein said composition is suitable for medicinal or cosmetic use.

69. (Amended) A composition comprising at least one oligonucleotide, said oligonucleotide comprising a phosphodiester backbone, and a physiologically acceptable carrier, wherein at least one of said oligonucleotides [is selected from the group] has a nucleotide sequence consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3 [and] or SEQ ID NO: 4, and

wherein at least one of said oligonucleotides comprises a 5' phosphate, and wherein said composition is suitable for medicinal or cosmetic use.

71. (Amended) A method of increasing p53 activity in epidermal cells, said method comprising topically administering an effective amount of $d(pT)_2$, or oligonucleotide having a nucleotide sequence consisting of SEQ ID NO:1 or SEQ ID NO:6 to said cells [a cell comprising contacting said cell with an effective amount of DNA fragments selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, dinucleotide dimers and combinations thereof; wherein said fragments are about 2 to about 200 nucleotides in length].

75. (Amended) A method of treating hyperproliferative disease affecting epithelial cells in a mammal, comprising administering to the epithelial cells [of interest in the mammal] an effective amount of a composition comprising at least one DNA [fragments] oligonucleotide comprising a phosphodiester backbone, wherein the oligonucleotide has a nucleotide sequence consisting of [selected from the group consisting of:] SEQ ID NO: 1, SEQ ID NO:6 or pTpT [SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4 and combinations thereof].

76. (Amended) The method of Claim 75, wherein [said DNA fragments are] pTpT is ultraviolet-irradiated.

83. (Amended) The method of Claim 75, wherein the epithelial cells [of interest] are carcinoma cells.

85. (Amended) A method of inhibiting proliferation of skin cells in a mammal, comprising administering topically to the skin cells [epidermis of the mammal] an effective amount of [DNA fragments selected from the group consisting of: single-stranded DNA fragments,] deoxynucleotides, dinucleotides, [and] or dinucleotide dimers and combinations thereof [wherein said DNA fragments are about 2 to about 200 nucleotides in length].

86. (Amended) A method of [preventing] inhibiting or reducing DNA damage in [a cell] epidermal cells of a mammal, wherein said DNA damage is caused by UV irradiation, said method comprising topically administering to the cells in the mammal [or DNA-damaging chemicals, comprising contacting said cell with] an effective amount of a composition comprising DNA fragments that are approximately 2-200 nucleotides in length, the DNA fragments being selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, [and] dinucleotide dimers and combinations thereof[; wherein said DNA fragments are about 2 to about 200 nucleotides in length].

88. (Amended) A method of treating malignant cells of a mammal, comprising [contacting] administering to said cells [with] an effective amount of DNA fragments that comprise a phosphodiester backbone and are about 2-200 nucleotides in length, the DNA fragments being selected from the group consisting of: single-stranded DNA fragments, deoxynucleotides, dinucleotides, [and] dinucleotide dimers and combinations thereof[; wherein said DNA fragments are about 2 to about 200 nucleotides in length].